

A pre-operative chemoembolization therapy using lipiodol, cisplatin and gelatin sponge for hepatocellular carcinoma

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Summary. The significance of pre-operative transcatheter arterial chemoembolization therapy using lipiodol, cisplatin and gelatin sponge (Gelfoam) for the prevention of the recurrence of hepatocellular carcinoma (HCC) was evaluated. On the 103 patients who underwent radical operations for HCC with a tumor size less than 10 cm, 52 patients received no pre-operative therapy (group C), and 51 patients received pre-operative chemoembolization using lipiodol, a chemotherapeutic agent and Gelfoam. Of these 51 patients, 37 patients received a combination of lipiodol, cisplatin and Gelfoam (group A), while the remaining 14 patients received lipiodol, adriamycin and Gelfoam (group B). The disease-free survival rates after surgery were compared between group A, group B and group C. The 2-year disease-free survival rates in group A, group B and group C were 72%, 46% and 54%, respectively. These rates therefore suggest that pre-operative chemoembolization using lipiodol, cisplatin and Gelfoam is a useful method to prevent the recurrence of HCC after surgery.

Introduction

The remarkable progress in imaging modalities for high-risk patients has made it possible to detect small hepatocellular carcinoma (HCC) at an early stage. However, HCC in Japan is very often associated with cirrhosis [3, 5].

In recent years, an improvement in the assessment of resectability, the concept of a limited operation [1] and a subsegmental or partial resection using intra-operative ultrasonography [4, 12] have led to a high degree of resectability and low operative mortality rates. However, the long-term survival rates after surgery are not yet satisfactory even at a relatively early stage [2, 8, 13]. The reason for these poor rates is believed to be related to the high recurrence rate in the residual liver because a cirrhotic liver limits the extent of a hepatic resection.

Recently, arterial embolization and chemoembolization have been considered useful therapeutic procedures for HCC. More recently, chemoembolization using lipiodol [7, 11] (ethidized oil, Laboratoire Guerbet, Aulnay, Kalamazoo, MI) has been recommended.

In this study, the significance of pre-operative chemoembolization using lipiodol for the prevention of a recurrence has been evaluated.

Patients and methods

A total of 132 patients with HCC had a radical hepatic resection at The Center for Adult Diseases, Osaka during a period until April 1987. Of the 132 patients, 14 patients either died within 1 month after operation or died in hospital, leaving 118 patients (89%) to be studied.

Surgery was defined as radical for the cases where all the gross disease was removed, including a disease-free resection margin. The 118 patients included 96 men (81%) and 22 women (19%), ranging in age from 35 to 75 years (mean \pm SD: 58 ± 9 years); of these, 92 (78%) had cirrhosis, 23 (19%) had chronic hepatitis and 3 patients (3%) had normal parenchyma.

Forty-four patients (37%) had a partial hepatic resection (Hr0), 31 patients (26%) had hepatic subsegmentectomy (HrS), 27 patients (23%) had hepatic segmentectomy (Hr1), and 16 patients (14%) had hepatic lobectomy or extended lobectomy.

After resection, α -fetoprotein assays, liver function tests, liver ultrasonography and chest X-rays were routinely carried out. When recurrences were suspected, the patients received a liver computed tomography, and were re-admitted to the hospital for hepatic angiography.

Results

Recurrence

By the end of August 1987, 54 of the 118 patients (46%) experienced recurrences. Of the 54 patients, the liver was the site of first recurrence in 49 patients (91%), while in 5 (9%) the recurrences were found in distant sites. Of the 49 patients with an intrahepatic recurrence, 25 patients (51%) had a recurrence within 1 year after surgery, 13 patients (27%) had a recurrence 1–2 years after surgery, 9 patients (18%) had a recurrence 2–3 years after surgery, while the remaining 2 patients had a recurrence more than 3 years after surgery (Fig. 1).

Extent of resection and the disease-free survival rates

To examine the effect of the extent of resection on the recurrence, disease-free survival rates after surgery were calculated.

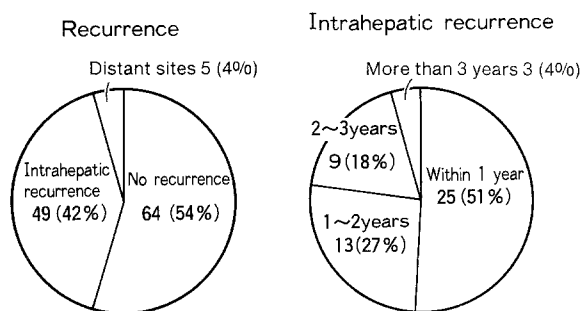


Fig. 1. The incidence of the intrahepatic recurrence and distant metastasis (left circle), and the interval up to the intrahepatic recurrence after surgery (right circle)

The extent of resection did not effect the disease-free survival rates for the groups with a tumor size either less than 5 cm or more than 5 cm (Fig. 2A, B).

Histological findings

Of the 103 patients with a tumor size less than 10 cm, 51 patients (50%) underwent chemoembolization using lipiodol, while the remaining 52 patients (50%) (group C) did not.

Chemoembolization, the combination of an intra-arterial infusion of a chemotherapeutic agent and arterial embolization, was performed under the following regimens: (a) by a gelatin sponge (Gelfoam) after the arterial infusion of 10–20 ml lipiodol containing 40–60 mg adriamycin (14 patients – group B); and (b) chemoembolization using a combination of 10–20 ml lipiodol, 2 mg/kg body weight of cisplatin and Gelfoam (37 patients – group A). A

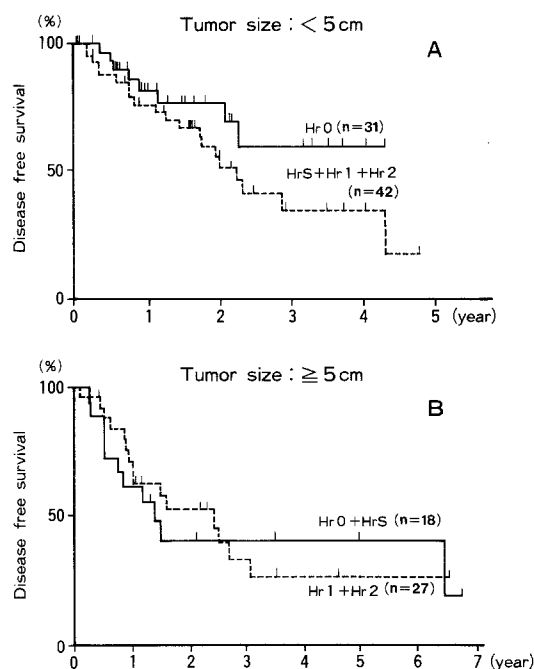


Fig. 2. The effect of the extent of a hepatic resection on the disease-free survival rates after surgery: the extent of the hepatic resection did not effect the disease-free survival rates. Hr0, partial resection; HrS, subsegmentectomy; Hr1, segmentectomy; Hr2, lobectomy or extended lobectomy

Table 1. Comparison of the necrotic effects (over 90% of the cancer cells were necrotic) on hepatocellular carcinoma between lipiodol (LPD), cisplatin (CDDP) and Gelfoam gelatin sponge, and LPD, adriamycin (ADM) and Gelfoam: LPD, CDDP and Gelfoam had a better necrotic effect than LPD, ADM and Gelfoam

Treatment	Main tumor	Daughter nodule	Tumor embolus in the portal vein
LPD + CDDP + Gelfoam	17/20 (85%)	10/13 (77%)	7/9 (78%)
LPD + ADM + Gelfoam	4/8 (50%)	2/5 (40%)	2/4 (50%)

hepatic resection was performed between 13 and 114 days after therapy.

The histological results are shown in Table 1. The ratio of patients in whom over 90% of the cancer cells were necrotic in the main tumor, daughter nodules and tumor emboli in the portal vein were 4/8 (50%), 2/5 (40%) and 2/4 (50%) in group B, and 17/20 (85%), 10/13 (77%) and 7/9 (78%) in group A, respectively.

Comparison of the disease-free survival rates between group A, group B and group C (Fig. 3)

The 1- and 2-year disease-free survival rates were 92% and 72% in group A, 67% and 46% in group B, and 70% and 54% in group C, respectively. Group A had the best disease-free survival rates among these three groups, and there was no difference in the disease-free survival rates between group B and group C.

Discussion

The extent of hepatic resection did not affect the incidence of recurrence of HCC (Fig. 2). This finding indicates that it is nearly impossible to control the cancerous lesions in patients within the limitations of the reserve capacity in patients with liver cirrhosis by hepatic resection alone.

To prevent a recurrence and to obtain a successful long-term survival rate after surgery for cirrhotic patients

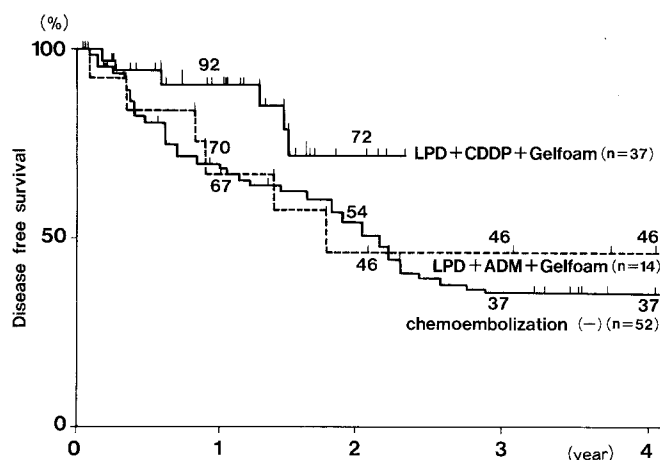


Fig. 3. Comparison of the disease-free survival rates among the three groups. The pre-operative chemoembolization group using lipiodol (LPD), cisplatin (CDDP) and Gelfoam gelatin sponge had the best disease-free survival rates. ADM, adriamycin

with HCC, we chose transcatheter arterial chemoembolization as the pre-operative therapy. Transcatheter arterial embolization (TAE) alone is quite effective for the main nodules, but has little effect on the daughter nodules and on the tumor emboli in the portal vein [9]. On the basis of these findings, TAE alone cannot be recommended as a curative treatment.

In 1983, Nakamura et al. [6] reported that the lipid lymphographic agent, lipiodol, injected into the hepatic artery, remained selectively in the hepatic tumor tissue for a long period. It has recently been discovered that lipiodol remains selectively not only in large tumors but also in daughter nodules. The method using lipiodol, cisplatin and Gelfoam [10] has a more necrotic effect on HCC as compared with lipiodol, adriamycin and Gelfoam (Table I).

In parallel with this finding, we found that the patients who underwent pre-operative chemoembolization using lipiodol, cisplatin and Gelfoam had better disease-free survival rates than the patients who underwent pre-operative chemoembolization using lipiodol, adriamycin and Gelfoam (Fig. 3).

We therefore now consider that pre-operative chemoembolization using lipiodol, cisplatin and Gelfoam is a useful method to prevent the recurrence of HCC after surgery.

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